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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TONGUE, LAKIA J	
ART UNIT	PAPER NUMBER
1645	
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02/02/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,873	KIRKBY ET AL.	
	Examiner	Art Unit	
	LAKIA J. TONGUE	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10,13,16-18,20,21,23,25-27,29-42,44-56,60 and 61* is/are pending in the application.

4a) Of the above claim(s) *29-31 and 35-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10,13,16-18,20,21,23,25-27,32-34,38-42,44-56,60 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 5, 2010 has been entered. Claims 1, 2, 4-10, 13, 16-18, 20, 21, 23, 25-27, 29-37, 38-42, 44-56, 60 and 61 are pending. Claims 1,5, 13, 17, 23, 27, 34, 44, 45, 50, 53-56 and 61 have been amended. Claims 29-31 and 35-37 have been previously withdrawn from further consideration as being drawn to non-elected inventions. Claims 11, 12, 14 and 15 were canceled in the initial response filed with the RCE. Claims 43 and 57-59 have been canceled in the supplemental response. Claims 1, 2, 4-10, 13, 16-18, 20, 21, 23, 25-27, 32-34, 38-42, 44-56, 60 and 61 are currently under examination.

Rejections Withdrawn

2. In view of Applicant's amendment, the rejection of claims 23, 56, 58 and 59 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (this is a new matter rejection) for the recitation of "an immunologically cross-reactive antigen..." (claim 23), "microparticles with an average

diameter of *not more* than 50 nm" (claim 56), "…rigid microparticles (claim 58)" and "case-like structures (claim 59)" is withdrawn. The cancellation of claims 58 and 59 renders said rejection moot.

3. In view of Applicant's cancellation of claim 59, the rejection of claims 1, 2, 4-10, 13, 16-18, 20, 21, 23, 25-27, 32-34 and 38-61 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention by the use of the terms "case-like structure" is withdrawn.

Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. The rejection of claims 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 46, 47, 49-55, 60 and 61 under 35 U.S.C. 102(b) as being anticipated by Foldvari et al. (WO 99/11247) is maintained for the reasons set forth in the previous office action. The cancellation of claims 43 and 57-59 renders the rejection of said claims moot.

Applicant argues that:

1) Foldvari does not disclose a construct for transdermal delivery comprising cationic sterols.

2) Foldvari discloses a composition of flexible lipid vesicles for transdermal administration of an immunogen, wherein a lipid vesicle is composed of lipid biolayers. Liposomes do not adopt the distinctive micro-particle structure in the form of a cage-like matrix typical of ISCOMS.

Applicant's arguments have been considered and are deemed non-persuasive.

The rejected claims are drawn to a construct for transdermal delivery of at least one immunogen to an individual comprising:

a) said at least one immunogen, or at least one expressible nucleic acid encoding said immunogen;

b) an occlusion vehicle and

c) an immunogen delivery system comprising: i) at least one cationic sterol and ii) at least one saponin, wherein said saponin forms a complex with said cationic sterol, and wherein said complex adopts a micro-particle structure in the form of a cage-like matrix; wherein, if the construct comprises said nucleic acid, said cationic sterol or said saponin interacts electrostatically or hydrophobically with said nucleic acid.

With regard to Point 1, contrary to Applicant's assertion, Foldvari discloses a construct comprising sterols such as cholesterol, which encompasses DC-cholesterol, which is a known cationic sterol. Absent evidence to the contrary, the sterol of Foldvari encompasses a cationic sterol.

With regard to Point 2, according to claim 1, when the saponin forms a complex with the cationic sterol it is at that point that said complex adopts a micro-particle structure in the form of a cage-like matrix. Foldvari discloses an immunogen delivery system comprising at least one cationic sterol and at least one saponin; the complex formed necessarily adopts a micro-particle structure in the form of a cage-like matrix, thus meeting the limitation of the claim.

As previously presented, Foldvari et al. disclose a biphasic lipid vesicle composition for transdermal administration. The transdermal device comprises a reservoir adapted to retain during storage and release in operation lipid vesicles containing an entrapped immunogen (see page 12, lines 18 and 19). The transdermal device includes a reservoir with a backing layer and membrane joined by an adhesive (see page 12, lines 22-25). Foldvari et al. disclose that the backing layer serves as a protective, impermeable covering to prevent loss of contents. Suitable backing materials include films for medical use (see page 12, lines 31-33). Foldvari et al. disclose that the device can be applied directly to the skin (see page 12, line 14). Foldvari et al. disclose that the reservoir includes lipid vesicles in suspension, and the lipid vesicles cross the membrane to contact and penetrate the skin for administration of the entrapped immunogen (see page 14, lines 13-15). Also, Foldvari et al. disclose that the membrane is designed to be a rate controlling membrane (see page 14, line 24).

Foldvari et al. disclose that the composition of the present invention includes a suspension containing an entrapped immunogen effective to elicit an immune response, e.g., for purposes of immunization or vaccination. In general, a wide variety of immunogens are suitable for use in the present invention, they include but are not limited to influenza virus antigens *Bordetella pertussis* antigens (such as pertussis toxin, filamentous haemagglutinin, pertaetin), human papilloma virus (HPV) antigens, *Helicobacter pylori* antigens, rabies antigens, tick-borne encephalitis (TBE) antigens, meningoccal antigens (such as capsular polysaccharides of serogroup A, B, C, Y and W-135), tetanus antigens (such as tetanus toxoid), diphtheria antigens (such as

diphtheria toxoid), pneumococcal antigens (such as *Streptococcus pneurnoniae* type 3 capsular polysaccharide), tuberculosis antigens, human immunodeficiency virus (HIV) antigens (such as GP-120, GP-160), cholera antigens (such as cholera toxin B subunit), 5 staphylococcal antigen (such as staphylococcal enterotoxin B), shigella antigens (such as shigella polysaccharides), vesicular stomatitis virus antigen (such as vesicular stomatitis virus glycoprotein), cytomegalovirus (CMV) antigens, hepatitis antigens (such as hepatitis A (HAV), B (HBV), C (HCV), D (HDV) and G (HGV) virus antigens, respiratory syncytial virus (KSV) antigens, herpes simplex antigens, or combinations thereof(e.g.,10 combinations of diphtheria, pertussis and tetanus (DPT)), antigens against anthrax and *Yersinia pestis* (see page 6, lines 22-33 and page 7, lines 1-13). Moreover, in addition to the vesicle-forming lipid component, the invention can include other lipid components capable of being incorporated into lipid bilayers, which for example can include sterols, saponin and Quil A (see page 8, lines 17-19 and 21; page 12, line 6). Foldvari et al. disclose that the adhesive layer that sticks to the skin is made from a pharmaceutically acceptable pressure sensitive adhesive (see page 13, lines 12-14). Foldvari et al. disclose that a wide variety of immunogens are suitable for use in the present invention, which include but are not limited to antigens derived from microorganisms, such as a virus, bacteria, parasite and/or fungus (see page 6, lines 27-33 and page 7, lines 1-20). Foldvari et al. discloses that the biphasic lipid vesicles of the invention include in the central core compartment of the lipid vesicle and in the aqueous space separating the lipid bilayers, an oil-in-water emulsion (see page 7, lines 23-25). Foldvari et al. disclose the use of enhancers such as monolauroyllysine or dipalmitoyllysine, an unsaturated fatty acid, such as oleic acid, a short chain fatty acid, such as lauric acid or methyl salicylate (see page 11, lines 15-19).

Since the Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The rejection of claims 1, 2, 4-6, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32-34, 38-42, 46-56, 60 and 61 under 35 U.S.C. 103(a) as being unpatentable over Foldvari et al. (WO 99/11247) and British Pharmacopoeia 1993 (Surgical Materials, 1996; 1943-1944) is maintained for the reasons set forth in the previous office action. The cancellation of claims 43 and 57-59 renders the rejection of said claims moot.

Applicant' argues that:

1) Nothing in Foldvari would lead the skilled person to consider the use of rigid microparticles in the form of a cage-like matrix.

2) Sterols disclosed in Foldvari are not cationic sterols, because none of them carry a net positive charge at pH 7.0.

3) Nothing in the BP reference cures the shortcomings of Foldvari, nor would the BP reference predictably lead a skilled person to the elements missing from Foldvari such as the requirement for an immunogen delivery system complex which assumes a microparticle structure in the form of a cage-like matrix and comprises a cationic sterol.

Applicant's arguments have been considered and are deemed non-persuasive.

The rejected claims are drawn to a construct for transdermal delivery of at least one immunogen to an individual comprising:

a) said at least one immunogen, or at least one expressible nucleic acid encoding said immunogen;

b) an occlusion vehicle and

c) an immunogen delivery system comprising: i) at least one cationic sterol and ii) at least one saponin, wherein said saponin forms a complex with said cationic sterol, and wherein said complex adopts a micro-particle structure in the form of a cage-like matrix; wherein, if the construct comprises said nucleic acid, said cationic sterol or said saponin interacts electrostatically or hydrophobically with said nucleic acid.

With regard to Points 1 and 2, the claims do not require the use of rigid microparticles in the form of a cage like matrix. The claims require that the saponin sterol complex adopts a microparticle structure in the form of a cage like matrix. Moreover, according to claim 1, when the saponin forms a complex with the cationic sterol it is at that point that said complex adopts a micro-particle structure in the form of a cage-like matrix. Foldvari discloses an immunogen delivery system comprising at least one cationic sterol and at least one saponin; the complex formed necessarily adopts a micro-particle structure in the form of a cage-like matrix, Thus meeting the limitation of the claim. Lastly, contrary to Applicant's assertion, Foldvari discloses a construct comprising sterols such as cholesterol, which encompasses DC-cholesterol, which is a known cationic sterol. Absent evidence to the contrary, the sterol of Foldvari is necessarily a cationic sterol. There is nothing in the specification that requires cationic sterols to carry a net positive charge at pH 7.0, nor is it a requirement of the claims.

With regard to Point 3, Foldvari, on its own discloses the limitations of claims 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 46, 47, 49-55, 60 and 61; the BP reference was only used to meet the limitations of claim 6, which recite that the occlusion vehicle is a hydrocolloid. This particular "shortcoming" is met by the use of the BP reference.

As previously presented, Foldvari et al. disclose a biphasic lipid vesicle composition for transdermal administration. The transdermal device comprises a reservoir adapted to retain during storage and release in operation lipid vesicles containing an entrapped immunogen (see page 12, lines 18 and 19). The transdermal device includes a reservoir with a backing layer and membrane joined by an adhesive (see page 12, lines 22-25). Foldvari et al. disclose that the backing layer serves as a protective, impermeable covering to prevent loss of contents. Suitable backing materials include films for medical use (see page 12, lines 31-33). Foldvari et al. disclose that the device can be applied directly to the skin (see page 12, line 14). Foldvari et al. disclose that the reservoir includes lipid vesicles in suspension, and the lipid vesicles cross the membrane to contact and penetrate the skin for administration of the entrapped immunogen (see page 14, lines 13-15). Also, Foldvari et al. disclose that the membrane is designed to be a rate controlling membrane (see page 14, line 24).

Foldvari et al. disclose that the composition of the present invention includes a suspension containing an entrapped immunogen effective to elicit an immune response, e.g., for purposes of immunization or vaccination. In general, a wide variety of immunogens are suitable for use in the present invention, they include but are not limited to influenza virus antigens *Bordetella pertussis* antigens (such as pertussis toxin, filamentous haemagglutinin, pertaetin), human papilloma virus (HPV) antigens, *Helicobacter pylori* antigens, rabies antigens, tick-borne encephalitis (TBE) antigens, meningoccal antigens (such as capsular polysaccharides of serogroup A, B, C, Y and W-135), tetanus antigens (such as tetanus toxoid), diphtheria antigens (such as diphtheria toxoid), pneumococcal antigens (such as *Streptococcus pneurnoniae* type 3

capsular polysaccharide), tuberculosis antigens, human immunodeficiency virus (HIV) antigens (such as GP-120, GP-160), cholera antigens (such as cholera toxin B subunit), 5 staphylococcal antigen (such as staphylococcal enterotoxin B), shigella antigens (such as shigella polysaccharides), vesicular stomatitis virus antigen (such as vesicular stomatitis virus glycoprotein), cytomegalovirus (CMV) antigens, hepatitis antigens (such as hepatitis A (HAV), B (HBV), C (HCV), D (HDV) and G (HGV) virus antigens, respiratory syncytial virus (KSV) antigens, herpes simplex antigens, or combinations thereof(e.g.,10 combinations of diphtheria, pertussis and tetanus (DPT)), antigens against anthrax and *Yersinia pestis* (see page 6, lines 22-33 and page 7, lines 1-13). Moreover, in addition to the vesicle-forming lipid component, the invention can include other lipid components capable of being incorporated into lipid bilayers, which for example can include sterols, saponin and Quil A (see page 8, lines 17-19 and 21; page 12, line 6). Foldvari et al. disclose that the adhesive layer that sticks to the skin is made from a pharmaceutically acceptable pressure sensitive adhesive (see page 13, lines 12-14). Foldvari et al. disclose that a wide variety of immunogens are suitable for use in the present invention, which include but are not limited to antigens derived from microorganisms, such as a virus, bacteria, parasite and/or fungus (see page 6, lines 27-33 and page 7, lines 1-20). Foldvari et al. discloses that the biphasic lipid vesicles of the invention include in the central core compartment of the lipid vesicle and in the aqueous space separating the lipid bilayers, an oil-in-water emulsion (see page 7, lines 23-25). Foldvari et al. disclose the use of enhancers such as monolauroyllysine or dipalmitoyllysine, an unsaturated fatty acid, such as oleic acid, a short chain fatty acid, such as lauric acid or methyl salicylate (see page 11, lines 15-19).

Foldvari et al. do not specifically disclose the use of a hydrocolloid adhesive or that one of the two compartments comprises a lyophilized pad comprising the immunogen and the other compartment comprises water or other appropriate solvent/diluent. Foldvari et al. do not specifically disclose that the cationic sterol is DC-cholesterol.

British Pharmacopoeia 1993 discloses wound dressings and medicated bandages, which include a semipermeable hydrocolloid dressing (see page 1943).

Foldvari et al. and British Pharmacopoeia 1993 disclose analogous inventions related to a product for transdermal delivery. It would have been obvious at the time the invention was made to use the hydrocolloid dressing of British Pharmacopoeia 1993 because it is a sterile, self-adhesive, waterproof, multi-component structure that would be effective in delivering at least one immunogen to an individual. Moreover, it would have been obvious at the time the invention was made to use the hydrocolloid because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Further, it would have been obvious to modify the compartments disclosed in Foldvari et al. to have the first compartment comprise a lyophilized pad comprising the immunogen and a second compartment comprise water or other appropriate solvent/diluent to help with preservation of the immunogen, inhibit the action of microorganisms and enzymes that would normally spoil or degrade the substance, to increase the shelf life and to quickly and easily rehydrate or reconstitute.

Moreover, with regard to claim 48, it would have been obvious to use DC-cholesterol because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

It would have been expected, barring evidence to the contrary, that the hydrocolloid dressing would be effective for transdermal delivery of at least one immunogen. KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obvious. See the recent Board decision *Ex parte Smith,--USPQ2d--,* slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR, 82 USPQ2d* at 1396).

With regard to claim 56, limitations such as the size of a microparticle are being viewed as limitations of optimizing experimental parameters. By all comparative data the composition of the prior art and the instantly claimed composition absent evidence to the contrary are one in the same.

6. The rejection of claims 1, 2, 4, 5, 7-9, 10, 13, 16-23, 25-27, 32-34, 38-42, 46, 47, 49-55, 60 and 61 under 35 U.S.C. 103(a) as being unpatentable over Foldvari et al. (WO 99/11247) and Lee et al. (International Journal of Pharmaceutics, 2001; 221: 1-22) is maintained for the reasons set forth in the previous office action. The cancellation of claims 43 and 57-59 renders the rejection of said claims moot

Applicant' argues that:

1) The Lee reference does not cure the shortcoming of Foldvari, nor would the Lee reference lead a skilled person to the elements missing from Foldvari such as the requirement for an immunogen delivery system complex which adopts a microparticle structure in the form of a cage-like matrix and comprises a cationic sterol.

Applicant's arguments have been considered and are deemed non-persuasive.

The rejected claims are drawn to a construct for transdermal delivery of at least one immunogen to an individual comprising:

a) said at least one immunogen, or at least one expressible nucleic acid encoding said immunogen;

b) an occlusion vehicle and

c) an immunogen delivery system comprising: i) at least one cationic sterol and ii) at least one saponin, wherein said saponin forms a complex with said cationic sterol, and wherein said complex adopts a micro-particle structure in the form of a cage-like matrix; wherein, if the construct comprises said nucleic acid, said cationic sterol or said saponin interacts electrostatically or hydrophobically with said nucleic acid.

With regard to Point 1, Foldvari, on its own discloses the limitations of claims 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 46, 47, 49-55, 60 and 61; the Lee reference was only used to meet the limitation of a hydrogel adhesive as Lee discloses that the use of hydrogels as drug carrier is widely known and used. This particular "shortcoming" is met by the use of the Lee reference.

Moreover, Foldvari discloses a construct comprising sterols such as cholesterol, which encompasses DC-cholesterol, which is a known cationic sterol. Absent evidence to the contrary, the sterol of Foldvari is necessarily a cationic sterol. There is nothing in the specification that requires cationic sterols to carry a net positive charge at pH 7.0, nor is it a requirement of the claims. Moreover, according to claim 1, when the saponin forms a complex with the cationic sterol it is at that point that said complex adopts a micro-particle structure in the form of a cage-like matrix. Foldvari discloses an immunogen delivery system comprising at least one cationic sterol and at least one saponin; the complex formed necessarily adopts a micro-particle structure in the form of a cage-like matrix, thus meeting the limitation of the claim.

As previously presented, Foldvari et al. disclose a biphasic lipid vesicle composition for transdermal administration. The transdermal device comprises a reservoir adapted to retain during storage and release in operation lipid vesicles containing an entrapped immunogen (see page 12, lines 18 and 19). The transdermal device includes a reservoir with a backing layer and membrane joined by an adhesive (see page 12, lines 22-25). Foldvari et al. disclose that the backing layer serves as a protective, impermeable covering to prevent loss of contents. Suitable backing materials include films for medical use (see page 12, lines 31-33). Foldvari et al. disclose that the device can be applied directly to the skin (see page 12, line 14). Foldvari et al. disclose that the reservoir includes lipid vesicles in suspension, and the

lipid vesicles cross the membrane to contact and penetrate the skin for administration of the entrapped immunogen (see page 14, lines 13-15). Also, Foldvari et al. disclose that the membrane is designed to be a rate controlling membrane (see page 14, line 24).

Foldvari et al. disclose that the composition of the present invention includes a suspension containing an entrapped immunogen effective to elicit an immune response, e.g., for purposes of immunization or vaccination. In general, a wide variety of immunogens are suitable for use in the present invention, they include but are not limited to influenza virus antigens *Bordetella pertussis* antigens (such as pertussis toxin, filamentous haemagglutinin, pertaetin), human papilloma virus (HPV) antigens, *Helicobacter pylori* antigens, rabies antigens, tick-borne encephalitis (TBE) antigens, meningoccal antigens (such as capsular polysaccharides of serogroup A, B, C, Y and W-135), tetanus antigens (such as tetanus toxoid), diphtheria antigens (such as diphtheria toxoid), pneumococcal antigens (such as *Streptococcus pneurnoniae* type 3 capsular polysaccharide), tuberculosis antigens, human immunodeficiency virus (HIV) antigens (such as GP-120, GP-160), cholera antigens (such as cholera toxin B subunit), 5 staphylococcal antigen (such as staphylococcal enterotoxin B), shigella antigens (such as shigella polysaccharides), vesicular stomatitis virus antigen (such as vesicular stomatitis virus glycoprotein), cytomegalovirus (CMV) antigens, hepatitis antigens (such as hepatitis A (HAV), B (HBV), C (HCV), D (HDV) and G (HGV) virus antigens, respiratory syncytial virus (KSV) antigens, herpes simplex antigens, or combinations thereof(e.g.,10 combinations of diphtheria, pertussis and tetanus (DPT)), antigens against anthrax and *Yersinia pestis* (see page 6, lines 22-33 and page 7, lines 1-13). Moreover, in addition to the vesicle-forming lipid component, the invention can include other lipid components capable of being incorporated into lipid bilayers, which for example can include sterols, saponin and Quil A (see page 8, lines 17-19 and 21; page 12, line 6). Foldvari et al. disclose that the adhesive layer that sticks to the skin is made from a pharmaceutically acceptable pressure sensitive adhesive (see page 13, lines 12-14). Foldvari et al. disclose that a wide variety of immunogens are suitable for use in the present invention, which include but are not limited to antigens derived from microorganisms, such as a virus, bacteria, parasite and/or fungus (see page 6, lines 27-

33 and page 7, lines 1-20). Foldvari et al. discloses that the biphasic lipid vesicles of the invention include in the central core compartment of the lipid vesicle and in the aqueous space separating the lipid bilayers, an oil-in-water emulsion (see page 7, lines 23-25). Foldvari et al. disclose the use of enhancers such as monolauroyllysine or dipalmitoyllysine, an unsaturated fatty acid, such as oleic acid, a short chain fatty acid, such as lauric acid or methyl salicylate (see page 11, lines 15-19).

Foldvari et al. do not specifically disclose the use of a hydrogel adhesive, cross-linked or otherwise, nor do they disclose that one of the two compartments comprises a lyophilized pad comprising the immunogen and the other compartment comprises water or other appropriate solvent/diluent.

Lee et al. disclose that hydrogels have been widely used as a drug carrier (see page 10; section 3.5)

Foldvari et al. and Lee et al. disclose analogous inventions related to a product for transdermal delivery. It would have been obvious at the time the invention was made to use a hydrogel because of its ease in manufacturing and self application (see Lee et al. Page 10). Moreover, it would have been obvious at the time the invention was made to use the cross-linked hydrogel because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Further, it would have been obvious to modify the compartments disclosed in Foldvari et al. to have the first compartment comprise a lyophilized pad comprising the immunogen and a second compartment comprise water or other appropriate solvent/diluent to help with preservation of the immunogen, inhibit the action of microorganisms and enzymes that would normally spoil or degrade the substance, to increase the shelf life and to quickly and easily rehydrate or reconstitute.

It would have been expected, barring evidence to the contrary, that the hydrogel would be effective for transdermal delivery of at least one immunogen. KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a

finding of obvious. See the recent Board decision *Ex parte Smith,--USPQ2d--,* slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR, 82 USPQ2d* at 1396).

By all comparative data the composition of the prior art and the instantly claimed composition absent evidence to the contrary are one in the same.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claim 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 44-55, 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foldvari et al. (WO 99/11247) as applied to claims 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 46, 47, 49-55, 60 and 61 above, and further in view of Kirkby et al. (U.S. 2004/0185057 A1).

The rejected claims are drawn to a construct for transdermal delivery of at least one immunogen to an individual comprising:

a) said at least one immunogen, or at least one expressible nucleic acid encoding said immunogen;

b) an occlusion vehicle and

c) an immunogen delivery system comprising: i) at least one cationic sterol and ii) at least one saponin, wherein said saponin forms a complex with said cationic sterol,

and wherein said complex adopts a micro-particle structure in the form of a cage-like matrix; wherein, if the construct comprises said nucleic acid, said cationic sterol or said saponin interacts electrostatically or hydrophobically with said nucleic acid.

Foldvari et al. disclose a biphasic lipid vesicle composition for transdermal administration. The transdermal device comprises a reservoir adapted to retain during storage and release in operation lipid vesicles containing an entrapped immunogen (see page 12, lines 18 and 19). The transdermal device includes a reservoir with a backing layer and membrane joined by an adhesive (see page 12, lines 22-25). Foldvari et al. disclose that the backing layer serves as a protective, impermeable covering to prevent loss of contents. Suitable backing materials include films for medical use (see page 12, lines 31-33). Foldvari et al. disclose that the device can be applied directly to the skin (see page 12, line 14). Foldvari et al. disclose that the reservoir includes lipid vesicles in suspension, and the lipid vesicles cross the membrane to contact and penetrate the skin for administration of the entrapped immunogen (see page 14, lines 13-15). Also, Foldvari et al. disclose that the membrane is designed to be a rate controlling membrane (see page 14, line 24).

Foldvari et al. disclose that the composition of the present invention includes a suspension containing an entrapped immunogen effective to elicit an immune response, e.g., for purposes of immunization or vaccination. In general, a wide variety of immunogens are suitable for use in the present invention, they include but are not limited to influenza virus antigens *Bordetella pertussis* antigens (such as pertussis toxin, filamentous haemagglutinin, pertaetin), human papilloma virus (HPV) antigens,

Helicobacter pylori antigens, rabies antigens, tick-borne encephalitis (TBE) antigens, meningoccal antigens (such as capsular polysaccharides of serogroup A, B, C, Y and W-135), tetanus antigens (such as tetanus toxoid), diphtheria antigens (such as diphtheria toxoid), pneumococcal antigens (such as *Streptococcus pneurnoniae* type 3 capsular polysaccharide), tuberculosis antigens, human immunodeficiency virus (HIV) antigens (such as GP-120, GP-160), cholera antigens (such as cholera toxin B subunit), 5 staphylococcal antigen (such as staphylococcal enterotoxin B), shigella antigens (such as shigella polysaccharides), vesicular stomatitis virus antigen (such as vesicular stomatitis virus glycoprotein), cytomegalovirus (CMV) antigens, hepatitis antigens (such as hepatitis A (HAV), B (HBV), C (HCV), D (HDV) and G (HGV) virus antigens, respiratory syncytial virus (KSV) antigens, herpes simplex antigens, or combinations thereof(e.g.,10 combinations of diphtheria, pertussis and tetanus (DPT)), antigens against anthrax and *Yersinia pestis* (see page 6, lines 22-33 and page 7, lines 1-13). Moreover, in addition to the vesicle-forming lipid component, the invention can include other lipid components capable of being incorporated into lipid bilayers, which for example can include sterols, saponin and Quil A (see page 8, lines 17-19 and 21; page 12, line 6). Foldvari et al. disclose that the adhesive layer that sticks to the skin is made from a pharmaceutically acceptable pressure sensitive adhesive (see page 13, lines 12-14). Foldvari et al. disclose that a wide variety of immunogens are suitable for use in the present invention, which include but are not limited to antigens derived from microorganisms, such as a virus, bacteria, parasite and/or fungus (see page 6, lines 27-33 and page 7, lines 1-20). Foldvari et al. discloses that the biphasic lipid vesicles of

the invention include in the central core compartment of the lipid vesicle and in the aqueous space separating the lipid bilayers, an oil-in-water emulsion (see page 7, lines 23-25). Foldvari et al. disclose the use of enhancers such as monolauroyllysine or dipalmitoyllysine, an unsaturated fatty acid, such as oleic acid, a short chain fatty acid, such as lauric acid or methyl salicylate (see page 11, lines 15-19).

Foldvari et al. do not specifically disclose that the complex of saponin and a cationic sterol adopts a microparticle structure in the form of a cage-like matrix (claim 1ii), that the immunogen comprises a peptide (claim 44), that the immunogen comprises a lipopeptide (claim 45) or that the cationic sterol is a DC-cholesterol (claim 48).

Kirkby et al. disclose transdermal applications of compounds which comprise immunogens such as peptides, lipopeptides, viruses, bacteria, nucleic acids and the like (see paragraphs 0051, 0056-76). Kirkby et al. disclose that the compounds comprise complexes comprising at least one sterol and at least one saponin (see paragraphs 0126-0132). Kirkby et al. disclose the use of Quil A (see paragraph 0111). Moreover, Kirkby et al. disclose that vehicles such as a posintro or a cationic ISCOM may be used and that in some embodiments will adopt a microparticle structure in the form of a cage-like matrix (see paragraphs 0124 and 0136). Lastly, Kirkby et al. disclose the use of cationic sterols such as DC-cholesterol (see paragraph 0219).

Foldvari et al. and Kirkby et al. disclose analogous inventions related to a product for transdermal delivery. It would have been obvious at the time the invention was made to use a peptide or lipopeptide or to use DC-cholesterol because Kirkby et al. and Foldvari et al. both disclose transdermal compositions comprising the same

components; also because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. See the recent Board decision *Ex parte Smith,--USPQ2d--,* slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR, 82 USPQ2d* at 1396).

It would have been expected, barring evidence to the contrary, that the use of a peptide, lipopeptide and/or DC-cholesterol would be effective in a composition for transdermal delivery of an immunogen. KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obvious. By all comparative data the composition of the prior art and the instantly claimed composition absent evidence to the contrary are one in the same.

8. Claims 1, 2, 4-6, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 44-56, 60 and 61 rejected under 35 U.S.C. 103(a) as being unpatentable over Foldvari et al. (WO 99/11247) and Kirkby et al. (U.S. 2004/0185057 A1) as applied to claims 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 44-55, 60 and 61 above, and further in view of British Pharmacopoeia 1993 (Surgical Materials, 1996; 1943-1944).

The rejected claims are drawn to a construct for transdermal delivery of at least one immunogen to an individual comprising:

a) said at least one immunogen, or at least one expressible nucleic acid encoding said immunogen;

b) an occlusion vehicle and

c) an immunogen delivery system comprising: i) at least one cationic sterol and ii) at least one saponin, wherein said saponin forms a complex with said cationic sterol, and wherein said complex adopts a micro-particle structure in the form of a cage-like matrix; wherein, if the construct comprises said nucleic acid, said cationic sterol or said saponin interacts electrostatically or hydrophobically with said nucleic acid.

The limitations of Foldvari et al. and Kirkby et al. are set forth above.

Foldvari et al. and Kirkby et al. do not specifically disclose that the occlusion vehicle is a hydrocolloid.

British Pharmacopoeia 1993 discloses wound dressings and medicated bandages, which include a semipermeable hydrocolloid dressing (see page 1943).

Foldvari et al., Kirkby et al. and British Pharmacopoeia 1993 disclose analogous inventions related to a product for transdermal delivery. It would have been obvious at the time the invention was made to use the hydrocolloid dressing of British Pharmacopoeia 1993 with the composition of Foldvari and Kirkby because the hydrocolloid dressing is a sterile, self-adhesive, waterproof, multi-component structure that would be effective in delivering at least one immunogen to an individual. Moreover, it would have been obvious at the time the invention was made to use the hydrocolloid as well as pick a peptide or lipopeptide because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Further, it would have been obvious to modify the compartments disclosed in Foldvari et al. to have the first compartment comprise a lyophilized pad comprising the immunogen and a second compartment comprise water or other appropriate solvent/diluent to help with preservation of the immunogen, inhibit the action of microorganisms and enzymes that would normally spoil or degrade the substance, to increase the shelf life and to quickly and easily rehydrate or reconstitute.

It would have been expected, barring evidence to the contrary, that the hydrocolloid dressing would be effective for transdermal delivery of at least one immunogen. KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obvious. See the recent Board decision *Ex parte Smith,--USPQ2d--,* slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR, 82 USPQ2d* at 1396).

With regard to claim 56, limitations such as the size of a microparticle are being viewed as limitations of optimizing experimental parameters. By all comparative data the composition of the prior art and the instantly claimed composition absent evidence to the contrary are one in the same.

9. Claims 1, 2, 4, 5, 7-9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 44-56, 60 and 61 rejected under 35 U.S.C. 103(a) as being unpatentable over Foldvari et al. (WO 99/11247) and Kirkby et al. (U.S. 2004/0185057 A1) as applied to claims 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-42, 44-55, 60 and 61 above, and further in view of Lee et al. (International Journal of Pharmaceutics, 2001; 221: 1-22).

The rejected claims are drawn to a construct for transdermal delivery of at least one immunogen to an individual comprising:

a) said at least one immunogen, or at least one expressible nucleic acid encoding said immunogen;

b) an occlusion vehicle and

c) an immunogen delivery system comprising: i) at least one cationic sterol and ii) at least one saponin, wherein said saponin forms a complex with said cationic sterol, and wherein said complex adopts a micro-particle structure in the form of a cage-like matrix; wherein, if the construct comprises said nucleic acid, said cationic sterol or said saponin interacts electrostatically or hydrophobically with said nucleic acid.

The limitations of Foldvari et al. and Kirkby et al. are set forth above.

Foldvari et al. and Kirkby et al. do not specifically disclose that the occlusion vehicle is a hydrogel adhesive or that the hydrogel adhesive is cross linked as recited in claims 7 and 8

Lee et al. disclose that hydrogels have been widely used as a drug carrier (see page 10; section 3.5).

Foldvari et al., Kirkby et al. and Lee et al. disclose analogous inventions related to a product for transdermal delivery. It would have been obvious at the time the invention was made to use a hydrogel of Lee et al. because of its ease in manufacturing and self application (see Lee et al. Page 10). Moreover, it would have been obvious at the time the invention was made to use the cross-linked hydrogel because all the claimed elements were known in the prior art and one skilled in the art

could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Further, it would have been obvious to modify the compartments disclosed in Foldvari et al. to have the first compartment comprise a lyophilized pad comprising the immunogen and a second compartment comprise water or other appropriate solvent/diluent to help with preservation of the immunogen, inhibit the action of microorganisms and enzymes that would normally spoil or degrade the substance, to increase the shelf life and to quickly and easily rehydrate or reconstitute.

It would have been expected, barring evidence to the contrary, that the hydrogel would be effective for transdermal delivery of at least one immunogen. KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obvious. See the recent Board decision *Ex parte Smith,--USPQ2d--,* slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR, 82 USPQ2d* at 1396). By all comparative data the composition of the prior art and the instantly claimed composition absent evidence to the contrary are one in the same.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKIA J. TONGUE whose telephone number is (571)272-2921. The examiner can normally be reached on Monday-Friday 8-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LJT
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/Vanessa L. Ford/

Primary Examiner, Art Unit 1645